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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,848	01/23/2006	Tatsuo Hoshino	21415 US C038435/0185665	2032

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EXAMINER	
LONG, SCOTT	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,848	HOSHINO ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-8 are pending. Claims 1-8 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 25 March 2005 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 23 May 2005 consisting of 1 sheet(s) are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statement(s).

Priority

This application claims benefit as a 371 of PCT/EP03/10574 (filed 09/23/2003). This application also claims benefit from EUROPEAN PATENT application 02021599.2

(filed 09/27/2002).The instant application has been granted the benefit date, 27 September 2002, from the European application 02021599.2.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 recites the limitation "the control sequences" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been

set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement;* (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 2 is broadly drawn, such that it applies to a genus of mutant yeasts derived from *Xanthophyllomyces dendrohous (Phaffia rhodozyma)* ATCC96815. The invention claims a genus of yeasts that comprise a large number of organisms with uncertain genetic structures. The specification teaches both spontaneous mutants of ATCC96815 and cells transformed by plasmids. However, the specification does not teach the necessary structure of these cells. From these two examples, it is clear that , the mutations can be situated in the host genome or on episomes. However, it is not possible for a skilled artisan to know the structure of the genetic mutations. In addition, spontaneous mutants of ATCC96815 may not be statutory subject matter, since there seems to be no hand-of-man involved in generating this organism.

Claim 5 is broadly drawn, such that it applies to a genus of DNA sequences that are "substantially homologous" to a β-carotene hydroxylase gene. While the specification teaches that the DNA sequences could share a minimum homology of 60% similarity to the β-carotene hydroxylase gene and exhibits the same enzymatic activity as the β-carotene hydroxylase gene from *Flavobacterium* R1534 (ATCC21588), the specification fails to detail the necessary structure of the substantially homologous

DNA sequences. The nature of which 60% homology is actually important for the claimed enzymatic function has not been described in the specification. In fact, even where the nucleic acid changes have no effect on protein structure or function, these sequences themselves represent allelic variations which have different diagnostic and therapeutic implications.

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Appellants are reminded adequate written description requires more than a mere statement that it is a part of the invention and reference to a potential method of isolating or using it. *See Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed Cir. 1991). In the instant case, the specification fails to describe the structure of the hairpin sequences capable of silencing any given gene, or fails to particularly point out, particularly pointing out critical consensus regions or motifs of the genus. What are the particular

sequences that can silence specific genes? Are there particular regions of the target genes that are most susceptible to the action of the hairpin? Thus it fails to provide adequate written description for the claimed genus.

Vas-Cath Inc. v. Mabhurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed genus of both (1) mutant yeasts derived from *Xanthophyllomyces dendrohous (Phaffia rhodozyma)* ATCC96815, and (2) DNA sequences that are "substantially homologous" to a β-carotene hydroxylase gene originated from *Flavobacterium* R1534 (ATCC21588).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brzostowicz et al. (US Patent 6,969,595, issued 29 November 2005) in view of Van Ooyen (US-5,840,528, issued 24 November 1998).

Claim 1 is directed to a process for producing zeaxanthin and β-cryptoxanthin which comprises cultivating a recombinant microorganism which is expressing a β-carotene hydroxylase gene and belonging to the genus *Xanthophyllomyces (Phaffia)*

in an aqueous nutrient medium under aerobic conditions, and isolating the resulted carotenoids from the cells of said recombinant microorganism or from the cultured broth.

Brzostowicz et al. teach "a method for the production of a carotenoid compound comprising...[transforming]...at least one isolated nucleic acid molecule encoding an enzyme in the carotenoid biosynthetic pathway under the control of suitable regulatory sequences...under suitable growth conditions...whereby an carotenoid compound is produced" (col 125, lines 44-57). Brzostowicz et al. further teach "the isolated nucleic acid molecule encodes...β-carotene hydroxylase" (col.126, lines 53-57). Brzostowicz et al. also teach, "the carotenoid compound is... β-cryptoxanthin,... zeaxanthin" (col.127, line 39 to col.128, line 5).

Brzostowicz et al. also teach the limitations of claims 3-8. Particularly, Brzostowicz et al. teach the limitation of claims 3-5, wherein the β-carotene hydroxylase gene is originated from *Flavobacterium* sp. ATCC21588 (col. 25, line 36). Brzostowicz et al. teach a method for producing zeaxanthin and β-cryptoxanthin, wherein the pH is "maintained constant at 6.95" (col. 57, line 18) and incubation times of 0-69.5 hours (table 15; col. 58, lines 35-45) and at an incubation temperature of 30°C.

Brzostowicz et al. do not teach the use of genus *Xanthophyllomyces (Phaffia)* as the recombinant microorganism use to express the recombinant proteins. Van Ooyen teaches transformed *Phaffia rhodozyma* capable of producing carotenoids, including zeaxanthin (col.2, line 50) through introduction of plasmid comprising a suitable gene, "crtZ"(col.5, line 62-63) into *Phaffia rhodozyma*. The

applicant will be familiar with the fact that "crtZ" is the name of the gene that encodes β-carotene hydroxylase. Van Ooyen teaches that the transformed *Phaffia* "is cultivated under conditions...the range of 15° - 26°C. The preferred range is 20° - 22°C." (col.6, line 24). Van Ooyen also teaches, "It is possible to produce other carotenoid precursors in the same way, in general all carotenoids that can enzymatically be derived from precursors of astaxanthin in *Phaffia* can be obtained" (col.6, lines 16-19).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to produce zeaxanthin and β-cryptoxanthin from recombinant *Phaffia* that expresses a β-carotene hydroxylase gene.

The person of ordinary skill in the art would have been motivated to make those modifications because *Phaffia rhodozyma* is a functionally equivalent microorganism that is useful for production of carotenoids. In fact, *Phaffia rhodozyma* is probably preferable over the methanotrophs of Brzostowicz et al., since "although single carbon substrates are cost effective energy sources [e.g. - methane], difficulty in genetic manipulation of these [methanotrophic] microorganisms... has limited their use primarily to the synthesis of native products" (Brzostowicz et al; col.2, line 67 to col. 3, line 4). Also, Van Ooyen teaches "Through cloning and expression of genes involved in the carotenoid biosynthetic pathway it also becomes possible to use *Phaffia rhodozyma* for obtaining desired carotenoids. Desired carotenoid production includes increased production of... carotenoids such as zeaxanthin (Van Ooyen; col.2, lines 45-51).

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Brzostowicz et al.. and Van Ooyen because each of these

teachings generated recombinant microorganisms which produced carotenoids, especially zeaxanthin and β-cryptoxanthin.

Therefore the method as taught by Brzostowicz et al. in view of Van Ooyen would have been *prima facie* obvious over the method of the instant application.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being obvious over Van Ooyen (WO1994/06918, published 31 March 1994) in view of Cunningham et al. (US-5,744,341, issued 28 April 1998).

The present application describes a process for producing zeaxanthin and β-cryptoxanthin which comprises cultivating a recombinant microorganism which is expressing a β-carotene hydroxylase gene (crtZ) and belonging to the genus Xanthophyllomyces (Phaffia) and isolating the resulting carotenoids from the cells of said recombinant microorganism or from the cultured broth.

Van Ooyen teaches Phaffia for carotenoid production (page 1, line 22 - page 2, line 29), and suggests that transformation of Phaffia with the crtZ gene can be used for the increased production of carotenoids, e.g. zeaxanthin (page 9, line 36 to page 10, line 6). In addition, the conditions for cultivation of the latter microorganism are disclosed (page 10, lines 30-36; page 11, lines 1-2; pages 12-17; page 21, lines 7-8).

Van Ooyen does not teach production of β-cryptoxanthin in Phaffia.

Cunningham et al. teach the production of zeaxanthin and β-cryptoxanthin by a microorganism that produces carotenoids and that was transformed with the β – carotene hydroxylase gene from A. thaliana (col.5, lines 35-39; col. 6, lines 37-45).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to produce zeaxanthin and β-cryptoxanthin in Phaffia.

The person of ordinary skill in the art would have been motivated to make that modification because, "Through cloning and expression of genes involved in the carotenoid biosynthetic pathway it also becomes possible to use *Phaffia rhodozyma* for obtaining desired carotenoids. Desired carotenoid production includes increased production of... carotenoids such as zeaxanthin," (Van Ooyen, page 4, lines 1-6) and Cunningham et al. seek "method for augmenting the accumulation of carotenoids and production of novel and rare carotenoids. The present invention provides methods for controlling the ratio of various carotenoids in a host." (Cunningham et al., col. 1, lines 11-15).

An artisan would have expected success, because transformation of genes into Phaffia is a well understood technology.

Therefore the method as taught by Van Ooyen in view of Cunningham et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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